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MORRISON & FOERSTER LLP
3811 VALLEY CENTRE DRIVE
SUITE 500
SAN DIEGO, CA 92130-2332

EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,819	STANLEY, CHRISTOPHER J.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 January 2001 (original)* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/313,385* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on September 28, 2004 has been entered. The claims pending in this application are claims 1 and 3-34. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of amendment filed on September 28, 2004.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 19 and 24-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 19 is rejected as vague and indefinite. Since the first part of claim 19 does not require a carrier macromolecule having a molecular weight in excess of 80,000 Daltons while the second part of claim 19 require a carrier macromolecule having a molecular weight in excess of 80,000 Daltons in order to perform the method recited in claim 18, the first part of claim 19 and the second part of claim 19 do not correspond each other. Please clarify.

5. Claim 24 is rejected as vague and indefinite in view of the phrase "hybridizing to said template having a sequence complementary to a portion of said template" because it is unclear what hybridizes to said template. Please clarify.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Walker (US Patent NO. 5,455,166, published on October 3, 1995).

Walker teaches strand displacement amplification.

Regarding claim 1, Walker teaches a method of amplification of a target nucleic acid sequence (and its complementary strand) in a sample by endonuclease mediated strand displacement. The method involves the steps of: 1) isolating nucleic acids suspected of containing the target sequence from a sample, 2) generating single stranded fragments of target sequences, 3) adding a mixture comprising (a) a nucleic acid polymerase, (b) deoxynucleosidetriphosphates including at least one substituted deoxynucleosidetriphosphate and (c) at least one primer which is complementary to a region at the 3' end of a target fragment and further wherein each primer has a sequence at the 5' end which is a recognition sequence for a restriction endonuclease, and 4) allowing the mixture to react for a time sufficient to generate reaction products (see column 4, last paragraph and column 5, first paragraph). Since Walker teaches adding a mixture comprising a nucleic acid polymerase, deoxynucleosidetriphosphates and at least one primer which is complementary to a region at the 3' end of a target fragment,

and allowing the mixture to react for a time sufficient to generate reaction products (see column 4, last paragraph and column 5, first paragraph) and bases of the primer is connected by 3', 5' phosphodiester bond, and the specification does not define "macromolecule" and it is known that OH- group is a nucleophilic functional group, Walker disclose providing a primer (two third of the primer with 5' phosphate) covalently bound to a carrier macromolecule (one third of the primer with 3'-OH), hybridizing the bound primer to said template (ie., a target fragment taught by Walker); and extending said primer to form an extended primer (ie., reaction products taught by Walker) which replicates from said template wherein said carrier macromolecule (one third of the primer) is water soluble at a temperature in the range of 0-60°C wherein said carrier macromolecule (one third of the primer with 3'-OH) is a synthetic polymer having nucleophilic functional groups as recited in claim 1.

Therefore, Walker teaches all limitations recited in claim 1.

Response to Arguments

In page 8, fourth paragraph of applicant's remarks, applicant argues that "Walker provides no disclosure of any process of using the carrier molecules recited in the claims. Walker also fails to provide any motivation for using the recited carrier molecules".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. Since bases of the primer is connected by 3', 5' phosphodiester bond and the specification does not define "macromolecule", one third of the primer with 3'-OH taught by Walker is considered as a carrier molecule in the rejection (a synthetic polymer having nucleophilic functional groups).

8. Claim 18 is rejected under 35 U.S.C. 102(b) as being anticipated by Bronstein (US Patent No. 5,220,005, published on June 15, 1993).

Regarding claim 18, Bronstein teaches to hybridize a DNA probe labeled with alkaline phosphatase with nucleic acids immobilized on a nitrocellulose membrane and detect the hybridization (see column 13, lines 44-61). Since alkaline phosphatase is directly and covalently attached to the DNA probe and it is known that alkaline phosphatase has a molecular weight in excess of 80,000 Daltons, the DNA probe taught by Bronstein is a first nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons (ie., alkaline phosphatase) as recited in the claim. Since it is known that cellulose is a complex carbohydrate, or polysaccharide consisting of 3,000 or more glucose units and glucose has a formula of ($C_6H_{12}O_6$) with a molecular weight of 180.2 Daltons (see an attachment for cellulose in previous office action mailed on January 7, 2004), a nucleic acid that is complementary with the DNA probe and is immobilized on a nitrocellulose membrane is a second nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons as recited in the claim. Since Bronstein teaches to hybridize a DNA probe labeled with alkaline phosphatase with nucleic acids immobilized on a nitrocellulose membrane and detect the hybridization (see column 13, lines 44-61), Bronstein discloses contacting said first and second nucleic acids under hybridization conditions and detecting hybridization between said first and second nucleic acids as recited in the claim.

Therefore, Bronstein teaches all limitations recited in claim 18.

Response to Arguments

In page 8, last paragraph bridging to page 9, first paragraph of applicant's remarks, applicant argues that "[C]laim 18 recites a method where two nucleic acid molecules are each bound to a non-nucleotide carrier molecule. Hybridization of the nucleic acids is detectable because of the interaction between the respective carrier molecules (e.g., see paragraph 47 of specification). Bronstein discloses the presence of alkaline phosphatase on only one of the nucleic acids in the hybridization. Thus, according to Bronstein, the nucleic acid cannot be detected by the interaction between the macromolecules, since only one is present and no interaction can therefore occur. Furthermore, Bronstein provides no motivation for supplying a second nucleic acid bound to a macromolecule".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because claim 18 does not require that the nucleic acid is detected by the interaction between the macromolecules as suggested by applicant. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

9. Claim 21 is rejected under 35 U.S.C. 102(e) as being anticipated by Gold *et al.*, (US Patent NO. 6,011,020, filed on May 4, 1995).

Regarding claim 21, since Gold *et al.*, teach to bind a complex formed by a nucleic acid and a PEG molecule to an ion exchange chromatography wherein the nucleic acid binds a PEG molecule by vinyl sulfone (see column 18, second paragraph and column 31, second paragraph) and PEG is synthetic polymer having nucleophilic functional groups (see the specification, page 8), Gold *et al.*, disclose an immobilized nucleic acid comprising a nucleic acid linked via one or

more moieties derived from divinyl sulfone to a non-nucleotide carrier macromolecule (ie., PEG), which the non-nucleotide carrier macromolecule is directly bound to a solid support (ie., the ion exchange chromatography taught by Gold *et al.*,) wherein the non-nucleotide carrier macromolecule is a synthethic polymer having nucleophilic functional groups (ie., PEG) as recited in claim 21.

Therefore, Gold *et al.*, teach all limitations recited in claim 21.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Walker (1995 in view of McCormick *et al.*, (Promega Notes Magazine Number 40, 1993, p.04).

The teachings of Walker have been summarized previously, *supra*.

Walker does not disclose that alkaline phosphatase (carrier macromolecule) is covalently bound to the primer although Walker teaches a primer labeled with alkaline phosphatase.

McCormick *et al.*, teach to use a primer covalently bound to alkaline phosphatase as a hybridization probe.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 1 using a primer covalently bound with a carrier macromolecule in view of the prior art of Walker and

McCormick *et al.*. One having ordinary skill in the art would have been motivated to do so because McCormick *et al.*, have successfully used a probe covalently bound alkaline phosphatase as a hybridization probe, and the simple replacement of one method for labeling a primer with alkaline phosphatase (ie., the method taught by Walker) from another method for labeling a primer with alkaline phosphatase (ie., the method taught by McCormick *et al.*,) during the process for making a primer recited in claim 1 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. In re Rose 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

12. Claims 3, 4, 7-9, 11, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker (1995) as applied to claim 1 above, and further in view of Gold *et al.*, (1995).

The teachings of Walker and Gold *et al.*, have been summarized previously, *supra*.

Walker teaches that said primer is extended by a polymerase wherein said polymerase incorporates nucleotides into said primer wherein said primer is extended in a strand displacement amplification and said template is a double stranded template and is denatured to a

single stranded form, said carrier macromolecule-bound primer is complementary in sequence to a region of one of the template strands and a second primer is provided which is complementary in sequence to a region of the other strand, which second primer is also extended so as to form a complementary sequence copy of said template second strand as recited in claims 8, 9, and 11 (see Figure 2 and column 9, last paragraph). Since the specification does not define "carrier macromolecule" and Walker teaches to use one or more detectable markers including enzymes and liposomes, it is obvious to one having ordinary skill in the art at the time the invention was made to label a second primer with a carrier macromolecule as recited in claims 13.

Walker does not disclose a primer covalently bound to a carrier macromolecule via one or more moieties derived from divinyl sulfone as recited in claims 3 and 7.

Gold *et al.*, teach a nucleic acid covalently bound to a carrier macromolecule (ie., PEG) via one or more moieties derived from divinyl sulfone (see column 18, second paragraph and column 31, second paragraph) wherein PEG is synthethic polymer having nucleophilic functional groups (see the specification, page 8).

Regarding claim 4, since it is known that PEG is water soluble with a structure of –(CH2-CH2-O)$_n$- and pH of 4.5-7 (see attachment for PEG), Gold *et al.*, disclose that the carrier macromolecule (ie., PEG) in its free state is substantially linear and substantially charged at a pH in the range of 4 to 10 as recited in claim 4.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 3 using a primer covalently bound to a carrier macromolecule (ie., PEG) via one or more moieties derived from divinyl sulfone wherein PEG is a synthetic polymer having nucleophilic functional groups

in view of the patents of Walker and Gold *et al.*. One having ordinary skill in the art would have been motivated to do so because Gold *et al.*, have successfully made a nucleic acid covalently bound to a carrier macromolecule (ie., PEG) via one or more moieties derived from divinyl sulfone and the simple replacement of one well known label (ie., alkaline phosphatase) from another well known label (i.e., PEG) during the process for making a primer recited in claim 3 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because both alkaline phosphatase and PEG are used as oligonucleotide labels.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. In re Rose 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

13. Claims 10, 12, and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker (1995) in view of Gold *et al.*, (1995) as applied to claim 1, 3, 4, 7-9, 11, and 13 above, and further in view of Landegren *et al.*, (US Patent No. 4,988,617, published on January 29, 1991).

The teachings of Walker and Gold *et al.*, have been summarized previously, *supra*.

Walker and Gold *et al.*, do not disclose that said primer is extended by the action of

a ligase ligating said primer to at least one another primer hybridized to said template as recited in claim 10, said carrier macromolecule is bound to a solid support as recited in claim 12, said another primer which is ligated by said ligase is also bound to a carrier macromolecule wherein during the extension, a detectable marker is incorporated into one of the extended primers as recited in claims 14 and 15, said extension of one of the primers is conducted *in situ* in a biological sample wherein said biological sample is a plant or animal tissue sample, microorganism culture, or microorganism culture medium as recited in claims 16 and 17.

Landegren *et al.*, teach a ligase chain reaction using two primers with different labels (see Figure 1, column 4, lines 12-50 , column 8, lines 43-46, and column 10, last paragraph). Since the specification does not define "carrier macromolecule" and biotin on one of the primers taught by Landegren *et al.*, is a carrier molecule and a detectable marker as recited in claims 14 and 15. Therefore, Landegren *et al.*, teach that said primer is extended by the action of a ligase ligating said primer to at least one another primer hybridized to said template as recited in claim 10, said another primer which is ligated by said ligase is also bound to a carrier macromolecule wherein during the extension, a detectable marker is incorporated into one of the extended primers as recited in claims 14 and 15. Since Landegren *et al.*, teach that, after ligation, the ligation product labeled with biotin is purified by streptavidin immobilized to a solid support (see columns 10 and 11), in view of teachings of Landegren *et al.*, Walker and Gold *et al.*, said carrier macromolecule (ie., PEG) taught by Gold *et al.*, is bound to a solid support as recited in claim 12. Since Landegren *et al.*, teach to use DNA from sickle cell patient for in situ analysis, Landegren *et al.*, disclose that said extension of one of the primers is conducted *in situ* in a

biological sample wherein said biological sample is a animal tissue sample as recited in claims 16 and 17.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 10, 14, and 15 in view of the patents of Walker, Gold *et al.*, and Landegren *et al.*, One having ordinary skill in the art would have been motivated to do so because Landegren *et al.*, have successfully extended a primer by ligase chain reaction using two primers with different labels and the simple replacement of one well known replication method (i.e., the method taught by Walker) from another well known replication method (i.e., the method taught by Landegren *et al.*,) during the process of performing the methods recited in claims 10, 12, and 14-17 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the method taught by Walker and the method taught by Landegren *et al.*, are functional equivalent methods which are used for the same purpose (ie., extending a primer).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

14. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Walker (1995) in view of Gold *et al.*, (1995) and Landegren *et al.*, (1991) as applied to claim 1, 3, 4, and 7-17

above, and further in view of Barany *et al.*, (US Patent NO. 6,027,889, priority date: May 28, 1996).

The teachings of Walker, Gold *et al.*, and Landegren *et al.*, have been summarized previously, *supra*.

Walker, Gold *et al.*, and Landegren *et al.*, do not disclose using the probe to detect the nucleic acid sequence in a sample by hybridization thereto as recited in claim 20 However, as shown above, Walker in view of Gold *et al.*, and Landegren *et al.*, teach making a probe for detecting said sequence by using said sequence as a template sequence in the method as claimed in claim 17 such that a probe comprises said extended primer that has a sequence complementary to said sequence to be detected is bound to said carrier macromolecule, removing any free nucleic acid not bound to said carrier macromolecule thereof as recited in claim 20.

Barany *et al.*, teach using the ligated probe to detect the nucleic acid sequence in a sample by hybridization (see Figure 1).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method in view of the patents of Walker, Gold *et al.*, Landegren *et al.*, and Barany *et al.*. One having ordinary skill in the art would have been motivated to do so because Barany *et al.*, have successfully used a ligated product as a probe for a hybridization assay (see Figure 1). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to use a ligated product recited in claim 17 as a probe for a hybridization assay.

15. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gold *et al.*, (1995) as applied to claim 1 above, and further in view of Urdea (US Patent No. 4,775,619,published on October 4, 1988).

The teachings of Gold *et al.*, have been summarized previously, *supra*.

Gold *et al.*, do not disclose formulating the immobilized nucleic acid recited in claim 21 as a hybridization probe and introducing the immobilized nucleic acid into a hybridization utilizing the hybridization probe as recited in claim 22.

Urdea teaches to perform a hybridization of a nucleic acid immobilized on a column to a sample containing a DNA fragment (see column 10, lines 40-58).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have formulated the immobilized nucleic acid recited in claim 21 as a hybridization probe and introduced the immobilized nucleic acid into a hybridization utilizing the hybridization probe in view of the patents of Gold *et al.*, and Urdea. One having ordinary skill in the art would have been motivated to do so because Urdea indicates that a nucleic acid immobilized on a column is used for hybridization with a sample containing a DNA fragment (see column 10, lines 40-58). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to formulate the immobilized nucleic acid recited in claim 21 as a hybridization probe and introduce the immobilized nucleic acid into a hybridization utilizing the hybridization probe.

16. Claims 3-6, 8, 9, 11, 13, 23, and 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Walker (1995) as applied to claim 1 above, and further in view of Westling *et al.*, (US Patnet No. 5,700,921, filed on November 27, 1995).

The teachings of Walker have been summarized previously, *supra*.

Regarding claim 4-6 and 34, since Walker teaches adding a mixture comprising a nucleic acid polymerase, deoxynucleosidetriphosphates and at least one primer which is complementary to a region at the 3' end of a target fragment, and allowing the mixture to react for a time sufficient to generate reaction products (see column 4, last paragraph and column 5, first paragraph) wherein the at least primer is labeled with alkaline phosphatase (see column 4, third paragraph), and it is known that alkaline phosphatase has a molecular weight in excess of 80,000 Daltons, and is water soluble with a pH of 7.6 (see attachment for alkaline phosphatase in the office action mailed on July 1, 2004), Walker disclose that the carrier macromolecule (ie., alkaline phosphatase) in its free state is substantially linear and substantially uncharged at a pH in the range of 4 to 10 wherein said carrier molecule has a peak molecular weight in the range of in excess of 80,000 to 4,000,000 Daltons and said carrier macromolecule has a molecular weight in excess of 80,000 Daltons as recited in claims 4-6 wherein alkaline phosphatase is a polypeptide as recited in claim 34.

Regarding claims 8, 9, 11, and 13, Walker teaches that said primer is extended by a polymerase wherein said polymerase incorporates nucleotides into said primer wherein said primer is extended in a strand displacement amplification and said template is a double stranded template and is denatured to a single stranded form, said carrier macromolecule-bound primer is complementary in sequence to a region of one of the template strands and a second primer is

provided which is complementary in sequence to a region of the other strand, which second primer is also extended so as to form a complementary sequence copy of said template second strand as recited in claims 8, 9, and 11 (see Figure 2 and column 9, last paragraph). Since the specification does not define "carrier macromolecule" and Walker teaches to use one or more detectable markers including enzymes and liposomes, it is obvious to one having ordinary skill in the art at the time the invention was made to label a second primer with a carrier macromolecule as recited in claims 13.

Walker does not disclose a primer bound to a carrier macromolecule via one or more moieties derived from divinyl sulfone wherein alkaline phosphatase is a polypeptide as recited in claims 3 and 23.

Westling *et al.,* teach that an oligonculeotide is bound to said carrier macromolecule(ie., alkaline phosphatase) via one or more moieties derived from divinyl sulphone (see columns 10 and 11).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 3 and 23 wherein said primer is bound to said carrier macromolecule(ie., alkaline phosphatase) via one or more moieties derived from divinyl sulphone in view of the patents of Walker and Westling *et al.*. One having ordinary skill in the art would have been motivated to do so because Westling *et al.*, have successfully bound an oligonculeotide to a carrier macromolecule(ie., alkaline phosphatase) via one or more moieties derived from divinyl sulphone, and the simple replacement of one well known method (i.e., the method taught by Walker) from another well known method (i.e., the method taught by Westling *et al.*,) during the process of bonding a

primer to a carrier macromolecule(ie., alkaline phosphatase) would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because bonding a primer to a carrier macromolecule taught by Walker and bonding a primer to a carrier macromolecule taught by Westling *et al.*, are functional equivalent methods which are used for the same purpose.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

Response to Arguments

In page 10, last paragraph bridging to page 11, first paragraph of applicant argues that "[W]alker provides no disclosure of a primer bound to a water-soluble carrier macromolecule via a divinyl sulfone moiety. Westling discloses nucleic acids capable of reacting with a label conjugated to a thiol-reactive group, not a disulfone moiety (or derivative thereof). Furthermore, Westling also fails to disclose the use of primers bound to a water-soluble carrier macromolecule, let alone methods for replicating a nucleic acid template using such primer".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, vinyl sulfones taught by Westling *et al.*, (see column 11) are derivatives of divinyl sulfone. Second, vinyl sulfones taught by Westling *et al.*, (see column 11) cover different of derivatives of vinyl sulfones and include divinyl sulfone. Third, Westling *et al.*, disclose a nucleic acid bound to a water-soluble carrier macromolecule (see column 11). Fourth, since

Walker in view of Westling *et al.*, teach all limitations of claims 3-6, 8, 9, 11, 13, 23, and 34, the rejection is maintained.

17. Claims 24-28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker (1995) and Westling *et al.*, (1995) as applied to claims 1, 3-6, 8, 9, 11, 13, 23, and 34 above, and further in view of Lihme *et al.*, (WO 93/01498, published on January 21, 1993).

The teachings of Walker and Westling *et al.*, have been summarized previously, *supra*.

Regarding claims 28 and 30, Walker teaches that said primer is extended in a strand displacement amplification and said template is a double stranded template and is denatured to a single stranded form, said carrier macromolecule-bound primer is complementary in sequence to a region of one of the template strands and a second primer is provided which is complementary in sequence to a region of the other strand, which second primer is also extended so as to form a complementary sequence copy of said template second strand as recited in claims 28 and 30 (see Figure 2 and column 9, last paragraph).

Walker and Westling *et al.*, do not disclose a primer bound to dextran as recited in claim 24.

Regarding claims 24 and 27, Lihme *et al.*, teach that a water-soluble polymeric carriers having covalently attached one or more moieties derived from divinyl sulfone is capable of reaction with an oligonucleotide having a functional group which is reactive towards said free vinyl group (see claim 1 in page 114 and claim 18 in page 116).

Regarding claims 25 and 26, Lihme *et al.*, teach that said dextran in its free state is substantially linear and substantially unchanged at a pH in the range of 4 to 10 wherein said dextran has a peak molecular weight in the range of 1,000 to 40,000,000 (see page 20).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 24-28 and 30 in view of the references of Walker, Westling *et al.*, and Lihme *et al.*. One having ordinary skill in the art would have been motivated to do so because Lihme *et al.*, suggest to incorporate a water-soluble polymeric carriers having covalently attached one or more moieties derived from divinyl sulfone (ie., dextran) to an oligonucleotide having a functional group which is reactive towards said free vinyl group (see claim 1 in page 114 and claim 18 in page 116) and the simple replacement of one kind of water-soluble polymeric carriers (i.e., alkaline phosphatase taught by Westling *et al.*,) from another kind of water-soluble polymeric carriers (i.e., dextran taught by Lihme *et al.*,) during the process of bonding a primer to a carrier macromolecule would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because both alkaline phosphatase and sugar (i.e., dextran) covalently link to a nucleic acid by derivation of divinyl sulfone and are exchangeable (see Lihme *et al.*, column 11).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. In re Rose 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

18. Claims 29 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker in view of Westling *et al.,* and Lihme *et al.,* as applied to claims 3-6, 8, 9, 11, 13, 23, 24-28, 30, and 34 above, and further in view of Landegren *et al.,* (US Patent No. 4,988,617, published on January 29, 1991).

The teachings of Walker, Westling *et al.,* and Lihme *et al.,* have been summarized previously, *supra*.

Walker and Gold *et al.,* do not disclose that said primer is extended by the action of a ligase ligating said primer to at least one further primer hybridized to said template as recited in claim 29, said carrier macromolecule is bound to a solid support as recited in claim 31, and said extension of one of the primers is conducted *in situ* in a biological sample wherein said biological sample is a plant or animal tissue sample, microorganism culture, or microorganism culture medium as recited in claims 32 and 33.

Landegren *et al.,* teach a ligase chain reaction using two primers with different labels (see Figure 1, column 4, lines 12-50 , column 8, lines 43-46, and column 10, last paragraph). Therefore, Landegren *et al.,* teach that said primer is extended by the action of a ligase ligating said primer to at least one another primer hybridized to said template as recited in claim 29. Since Landegren *et al.,* teach that, after ligation, the ligation product labeled with biotin is purified by streptavidin immobilized to a solid support (see columns 10 and 11), in view of

teachings of Landegren *et al.*, Walker, Westling *et al.*, and Lihme *et al.*, said carrier macromolecule (ie., dextran) taught by Lihme *et al.*, is bound to a solid support as recited in claim 31. Since Landegren *et al.*, teach to use DNA from sickle cell patient for in situ analysis, Landegren *et al.*, disclose that said extension of one of the primers is conducted in situ in a biological sample wherein said biological sample is a animal tissue sample as recited in claims 32 and 33.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 29 and 31-33 in view of the patents of Walker, Westling *et al.*, Lihme *et al.*, and Landegren *et al.*, One having ordinary skill in the art would have been motivated to do so because Landegren *et al.*, have successfully extended a primer by ligase chain reaction using two primers with different labels and the simple replacement of one well known replication method (i.e., the method taught by Walker) from another well known replication method (i.e., the method taught by Landegren *et al.*,) during the process of performing the methods recited in claims 29 and 31-33 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the method taught by Walker and the method taught by Landegren *et al.*, are functional equivalent methods which are used for the same purpose (ie., extending a primer).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

Conclusion

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. No claim is allowed.

21. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703)872-9306 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
December 20, 2004

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
12/22/04